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Genetic and neuroanatomic associations in sporadic frontotemporal lobar degeneration

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ABSTRACT

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) that are sensitive for tau or TDP-43 pathology in frontotemporal lobar degeneration (FTLD). Neuroimaging analyses have revealed distinct distributions of disease in FTLD patients with genetic mutations. However, genetic influences on neuroanatomic structure in sporadic FTLD have not been assessed. In this report, we use novel multivariate tools, Eigenanatomy, and sparse canonical correlation analysis to identify associations between SNPs and neuroanatomic structure in sporadic FTLD. Magnetic resonance imaging analyses revealed that rs8070723 (*MAPT*) was associated with gray matter variance in the temporal cortex. Diffusion tensor imaging analyses revealed that rs1768208 (*MOBP*), rs646776 (near *SORT1*), and rs5848 (*PGRN*) were associated with white matter variance in the midbrain and superior longitudinal fasciculus. In an independent autopsy series, we observed that rs8070723 and rs1768208 conferred significant risk of tau pathology relative to TDP-43, and rs646776 conferred increased risk of TDP-43 pathology relative to tau. Identified brain regions and SNPs may help provide an in vivo screen for underlying pathology in FTLD and contribute to our understanding of sporadic FTLD.

1. Introduction

There is increasing neuroimaging evidence that genetic factors influence gray matter (GM) and white matter (WM) neuroanatomy in Alzheimer's disease (AD; Jahanshad et al., 2013; Shen et al., 2010). Genome-wide association (GWA) studies of autopsy-confirmed neurodegenerative disease cases have related several single nucleotide polymorphisms (SNPs) to the risk of accumulating specific types of histopathologic abnormality. In this study, we combine our knowledge of the genetic basis for frontotemporal lobar degeneration (FTLD; DeJesus-Hernandez et al., 2011; Höglinger et al., 2011; Renton et al., 2011; Van Deerlin et al., 2010) with neuroimaging in an effort to identify novel genetic and neuroanatomic associations that may be used to improve the diagnostic accuracy of FTLD. We additionally introduce a data-driven technique for investigating genetic and neuroanatomic associations that provides a novel approach for biomarker discovery.

FTLD is a common cause of early-onset neurodegenerative dementia. Approximately 20% of familial FTLD patients have a genetically identified mutation (Wood et al., 2013). Autopsy studies of FTLD have demonstrated that the vast majority of patients have either tau inclusions (FTLD-tau) or a TDP-43 proteinopathy (FTLD-TDP; Mackenzie et al., 2010). SNPs have been

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identified through case-control GWA or other association studies of autopsy-confirmed FTLD-tau (Höglinger et al., 2011) and FTLD-TDP (Renton et al., 2011; Van Deerlin et al., 2010) but have not been evaluated comparatively in FTLD-tau relative to FTLD-TDP. Neuroimaging studies suggest distinct neuroanatomic distributions of disease in FTLD-tau and FTLD-TDP (Seltman and Matthews, 2012; Whitwell et al., 2011b), and small sample studies have shown distinct anatomic distributions of GM and WM disease associated with genetic mutations (Rohrer et al., 2010; Whitwell et al., 2012). Diffusion tensor imaging (DTI) studies of WM achieve high sensitivity and specificity for predicting FTLD-tau or FTLD-TDP in patients with known pathology or genetic mutations, and these findings were validated in a detailed neuropathologic examination (McMillan et al., 2013). This observation is also consistent with previous neuropathologic reports suggesting that FTLD-tau has relatively increased WM disease compared with FTLD-TDP (Forman et al., 2002; Geser et al., 2009).

In this study, we combine SNPs with GM and WM neuroimaging to evaluate the hypothesis that genetic risk factors, or SNPs, may be reflected in differential brain morphology of sporadic FTLD-tau or FTLD-TDP. Although traditional approaches to biomarker discovery typically involve retrospective studies of gold standard autopsy-proven cases, we use a data-driven prospective approach that takes advantage of high-powered, multivariate statistics (see Fig. 1 for a schematic diagram). Our novel approach for biomarker discovery integrates neuroimaging and genetic markers in FTLD using 2 approaches. Eigenanatomy uses dimensionality reduction to identify anatomically constrained correlated voxels that account for the greatest variance in the entire data set and thus minimizes multiple comparison problems that are common in voxelwise neuroimaging studies (Avants et al., 2012; McMillan et al., 2013). We also use sparse canonical correlation analysis (SCCAN) for the multivariate integration of imaging and genetics by identifying correlations across independent matrices of data (Avants et al., 2010). We first evaluate the hypothesis that GM and WM neuroanatomic structure are related to genetic variation in sporadic FTLD patients. We then evaluate the hypothesis that SNPs associated with neuroanatomic structure confer risk for a specific histopathologic subtype of FTLD pathology in a large independent, autopsy-confirmed cohort of sporadic FTLD.

2. Methods

2.1. Neuroimaging participants

Ninety-two patients were recruited from the Penn Frontotemporal Degeneration Center at the University of Pennsylvania and diagnosed with a FTLD-spectrum neurodegenerative disease by a board-certified neurologist using published criteria (see Supplementary Table 1 for clinical phenotypes). The patient cohort comprised 37 women and 55 men who had an overall mean age of 63.20 years (SD = 8.51), mean disease duration of 4.09 years (SD = 2.54), and mean education of 15.43 years (SD = 2.95). All patients and their caregivers participated in an informed consent procedure approved by University of Pennsylvania Institutional Review Board.

All patients selected for this study were screened for research participation using an autopsy-validated cerebrospinal fluid ratio of total-tau to beta-amyloid <0.34, which has been cross-validated across 2 independent autopsy series and achieves 95.5% accuracy of screening FTLD and AD (Irwin et al., 2012b). To investigate sporadic FTLD, we additionally excluded patients who had a known genetic mutation that has been associated with FTLD-TDP, including *GRN* (Baker et al., 2006) and *C9orf72* expansions (DeJesus-Hernandez et al., 2011; Renton et al., 2011), or with an FTLD-tau associated *MAPT* mutation (Hutton et al., 1998). We further classified our cases using a previously published pedigree classification criteria (Wood et al., 2013): cases with a "medium" ($n = 9$) or low ($n = 7$) family history were negative for C9orf72 expansions, *GRN,* and *MAPT* and have a <12% chance of having a mutation detected (Wood et al., 2013); only 3 of our cases had a "high" family history and were negative when screened for 43 genetic mutations previously associated with neurodegenerative diseases; the remaining cases were either rated as "apparent sporadic" or had too small of a family to accurately determine family history. By omitting cases with genetic mutations, we also minimized overlap of cases previously reported in DTI and GM analyses of individuals with genetic or autopsy-confirmed FTLD (McMillan et al., 2013; only 3 autopsy cases from the previous report were included in the current study: 1 corticobasal degeneration [CBD]; 1 FTLD-TDP, and 1 FTLD-amyotrophic lateral sclerosis [ALS]).

2.2. Independent autopsy series

We queried the Penn Brain Bank for autopsy samples that had a primary neuropathologic diagnosis of FTLD-tau, including progressive supranuclear palsy (PSP), CBD, Pick disease, and argyrophilic grain disease or a diagnosis of FTLD-TDP, including FTLD with TDP-43 inclusions or ALS. Neuropathologic diagnoses were established according to consensus criteria (Mackenzie et al., 2010) by an expert neuropathologist (JQT) using immunohistochemistry with established monoclonal antibodies specific for pathogenic tau (mAb PHF-1; Otvos et al., 1994) and TDP-43 (mAbs p409/410 or 171; Lippa et al., 2009; Neumann et al., 2009). Patients who were included in the neuroimaging analysis were excluded from the independent autopsy series analysis. We further excluded cases with a secondary neuropathologic diagnosis (e.g., AD, vascular disease) or a known FTLD genetic mutation: all FTLD-tau cases were screened for *MAPT* mutations; all FTLD-TDP patients were screened for *GRN* mutations and a *C9orf72* expansion. This resulted in 153 sporadic FTLD-spectrum patients, FTLD-tau ($n = 62$) and FTLD-TDP ($n = 91$; see Supplementary Table 2).

2.3. Genetic analysis

We selected 21 SNPs from a custom-designed Pan-Neurodegenerative Disease-oriented Risk Allele panel (PANDoRA Version 1; Table 1) previously associated with FTLD-TDP or FTLD-tau in case-control GWA studies (Carrasquillo et al., 2010; Höglinger et al., 2011; Van Deerlin et al., 2010) or previously implicated in FTLD (Rademakers et al., 2008, 2005). The panel was designed using MassARRAY Assay design software in 2 multiplex reactions with 27 and 24 SNV respectively. See Supplementary Data for detailed genotyping methods. Each SNP was coded using an additive model, where 0 = homozygous for the nonrisk allele, 1 = heterozygous for the risk allele, and 2 = homozygous for the risk allele. "Risk allele" refers to the allele previously associated with disease risk in previous case-control studies.

2.4. Neuroimaging analysis

High-resolution volumetric (1 mm^3) magnetic resonance imaging volumes and diffusion-weighted images were acquired and preprocessed using a previously described pipeline with ANTs software (see Supplementary Data for details; Avants et al., 2011; McMillan et al., 2013). To analyze GM density and fractional anisotropy (FA) of WM, we used Eigenanatomy (available for free download in ANTs; https://github.com/stnava/sccan; Avants et al., 2012; McMillan et al., 2013). Eigenanatomy involves identifying